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# Combining ab initio calculations and Fourier-transform infrared (FT-IR) spectroscopy for quantitative analysis of multicomponent systems in solution: Tautomer proportions of ethyl acetoacetate

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ABSTRACT

A quantitative analysis method, combined experimental–computational approach (CECA), has been developed and applied for the detection of tautomer ratios of ethyl acetoacetate (eaa) in three organic solvents (acetonitrile, methanol, and chloroform). In order to obtain the relative concentrations of tautomers of eaa, IR intensities of both tautomers have been calculated at three different calculation levels (B3LYP/6-311++G(2d,2p), MP2/cc-pVDZ, and MP2/cc-pVTZ), augmented by the data obtained using basis set extrapolation technique. Experimental absorption bands were recorded at specific wavenumbers with FT-IR spectrophotometer and combined with calculated IR intensities in Lambert–Beer equation. Though the pure computational approach does not provide accurate values of the tautomers' ratio, yet the results obtained using the CECA method are very close to the experimental data.



## 1. Introduction

Tautomerism is an important phenomenon for organic chemistry, molecular biology, medicinal chemistry and biochemistry [1]. Very often understanding biochemical activity requires an advanced knowledge of tautomerization [2]. Many biochemical molecules, like amino acids and pyrimidine bases are characterized by existence of various tautomeric forms [3,4]. In these cases, conclusive explanation of the chemical reactivity is quite difficult without possessing qualitative and quantitative information about tautomers [5–7].

The molecular structure of single carbonyls, as well as of open chain 1,3-dicarbonyls, highly depends on tautomerization and has been the subject of many investigations [8–14]. The keto–enol ratio is very sensitive and depends on temperature, solvent properties and substitutions [15]. Intramolecular hydrogen bond and conjugated $\pi$ systems (Fig. 1) are the factors which stabilize the enol structure in open chain 1,3-dicarbonyls [16]. In the symmetric open chain 1,3-dicarbonyls, like acetylacetone, there is one possible keto and enol structure. However, in the case of asymmetric open chain 1,3-dicarbonyls such as in ethyl acetoacetate (eaa) two enol structures are possible (Fig. 1).

Eaa is ethyl ester of acetoacetic acid, which is usually prepared through the base-mediated condensation of ethyl acetate and has been frequently used in synthesis of many popular compounds such as amino acids, analgesics, antibiotics, vitamins, fructone and metal complexes [17–21]. The tautomerization of asymmetric 1,3-dicarbonyls has been studied by many scientists and eaa is one of the most popular compounds in this group [22–27]. Although two enol tautomers are possible for eaa, only one of them is detected as 7.5% component of the mixture in neat liquid [28].

The enolization of eaa is solvent dependent, as in case of many other tautomeric species. Relative enol concentration of eaa has been detected as 15–30% in nonpolar solvents such as carbon tetrachloride or benzene, 5% in acetone and 1% in water [29].

Detection of tautomer proportions in solution is quite difficult because of the isolation problems of a single tautomer and fast interconversion between different tautomeric forms. For this purpose the $^1$H NMR is one of the most frequently used experimental methods because from such experiments it is possible to obtain quantitative information for each tautomer [8]. Though $^1$H NMR is a very useful method for the detection of tautomer proportions it has serious disadvantages, such as insufficient time scale, cost of equipment and deuterated solvents, and lack of the deuterated forms of some solvents (e.g. hexane) [9].

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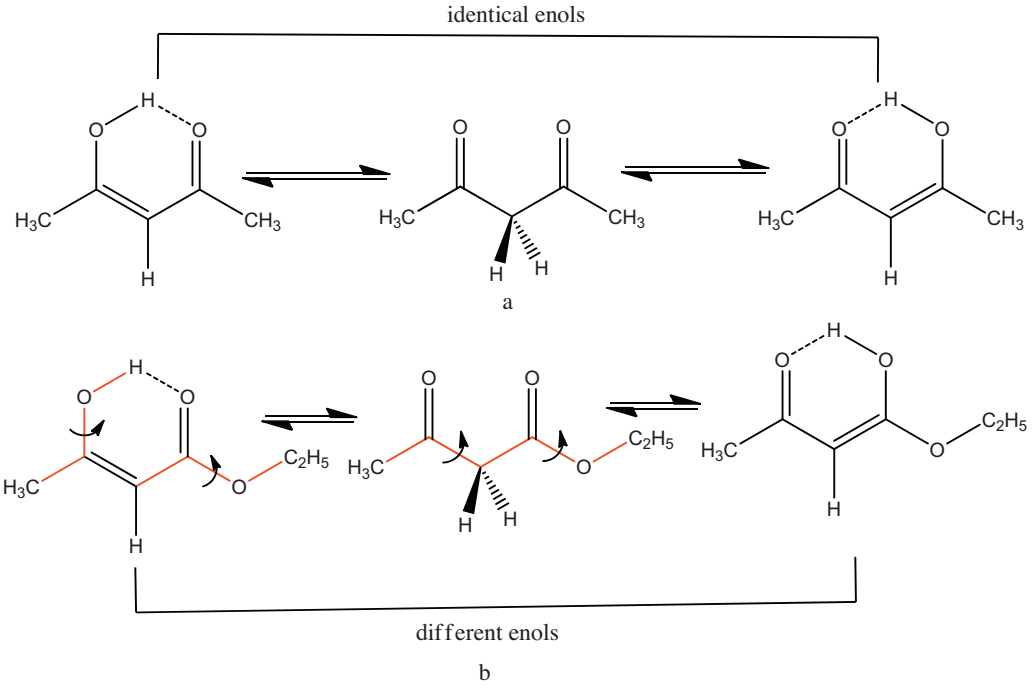


**Fig. 1.** Tautomerization of acetylacetone (a) and ethyl acetoacetate (b) (Red colored bonds represent the selected dihedrals while performing scan calculations.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In two previous papers, a novel method (combined experimental–computational approach – CECA) was used in order to investigate tautomer proportions of acetylacetone [9] and dimedone [30] in organic solvents. The CECA method is based on the link between two Lambert–Beer equations. Experimental absorptions and calculated IR intensities were used to determine tautomer proportions. The present work focuses on the investigations of the accuracy of the proposed CECA approach, including the effect of different calculation levels and basis set extrapolation. Based on the obtained results, the tautomers' ratio of eaa in different solutions at ambient temperature is estimated more accurately.

## 2. Materials and methods

All solvents and eaa were purchased from Aldrich or Fluka as analytical purity compounds. The FT-IR spectra of eaa were recorded using a Perkin Elmer Spectrum 60 spectrophotometer in 0.015 mm path length $CaF_2$ liquid cell with an average 32 scans, at 4 $cm^{-1}$ resolution and 1 $cm^{-1}$ interval. The concentrations of the eaa were 0.15 mol/L for all the measurements.

Calculations were performed with the Gaussian 09 [31] set of programs. The geometry optimizations and frequency calculations of tautomers of eaa were carried out at the B3LYP/6-311++G(2d,2p) [32–35], MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ [36,37] levels of theory with the conductor-like polarizable continuum model (CPCM) [38] for all the considered solvents (methanol, acetonitrile, and chloroform). It should be noted that the tautomer studies requires well defined solvent modeling techniques and accuracy of this investigation can be increased by using different models [39].

The input geometries have been created with Gaussview 5.0 and the best conformations for optimization were selected from the global minimum of the 3D potential energy surface obtained at the AM1 level. Two dihedral angles have been chosen for each tautomer (colored red at Fig. 1) to rotate 360 degrees and a scan calculation has been performed with 18 degrees and 20 steps for both dihedral angles. The rest of the molecules have been allowed to relax.

The CECA method developed for the studies of tautomers' ratio has been extensively explained in two recent publications [9,30]. This method is based on application of the well-known Lambert–Beer equation (Eq. (1)):

$$A_\nu = \varepsilon_\nu \cdot l \cdot c \tag{1}$$

$A_\nu$ and $\varepsilon_\nu$ are the absorbance and molar absorption coefficient (epsilon) values for specific wavenumber (absorbance maxima), respectively. $l$ is the path length and $c$ is concentration. Eq. (1) can be transformed to Eq. (2) for multi component systems.

$$AT_\nu = (\varepsilon_{1\nu} \cdot l \cdot c_1) + (\varepsilon_{2\nu} \cdot l \cdot c_2) + \dots \tag{2}$$

$AT_\nu$ is the total absorbance, $\varepsilon_{1\nu}$ and $\varepsilon_{2\nu}$ are the epsilons at a specific wavenumber ($\nu$), $c_1$ and $c_2$ are relative concentrations of each species. If Eq. (2) is applied to a keto–enol system at two different frequencies, one of them is a key band for keto and the other is for enol form. Subsequently, Eqs. (3) and (4) can be derived. A key band should be as free as possible from overlapping with the bands of other tautomer and these bands can be detected by comparison of calculated and experimental IR spectra [40].

$$AT\mathrm{k}_\nu = (\varepsilon\mathrm{k}_\nu \cdot l \cdot c\mathrm{k}) + (\varepsilon\mathrm{e}_\nu \cdot l \cdot c\mathrm{e}) = (\varepsilon\mathrm{k}_\nu \cdot l \cdot c\mathrm{k}) + 0 \tag{3}$$

$$AT\mathrm{e}_\nu = (\varepsilon\mathrm{k}_\nu \cdot l \cdot c\mathrm{k}) + (\varepsilon\mathrm{e}_\nu \cdot l \cdot c\mathrm{e}) = 0 + (\varepsilon\mathrm{e}_\nu \cdot l \cdot c\mathrm{e}) \tag{4}$$

As it can be seen from Eqs. (3) and (4) the contribution of keto tautomer is "0" for the enol key band and the contribution of enol is "0" for keto key band. The final Eq. (5) represents the ratio of Eqs. (3) and (4). The path length ($l$) can be eliminated from this relationship because both of these equations describe the same FT-IR experiment.

$$AT\mathrm{k}_\nu / AT\mathrm{e}_\nu = (\varepsilon\mathrm{k}_\nu \cdot c\mathrm{k})/(\varepsilon\mathrm{e}_\nu \cdot c\mathrm{e}) \tag{5}$$

Experimental absorbances and calculated IR intensities (instead of epsilon) were used to obtain relative ratio of eaa tautomers in Eq. (5). Since the same calculation methods were used to model both the keto and enol tautomers, one could assume that the difference between the calculated IR intensities and the experimental